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Developing resistance to drugs against MRSA

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Across the world, vancomycin has shown a surprising resilience to being displaced as the first choice treatment for serious MRSA infection. With the first description of low level resistance (VISA and hVISA in the late 1990s) an urgency to develop new MRSA drugs developed, further stimulated by the emergence of high level vancomycin resistance in the early 2000s. High level resistance hasn't become a clinical problem yet and VISA has, arguably, not emerged as a significant problem either. What is much more significant numerically, and probably even clinically are hVISA and so-called MIC creep or leap, with vancomycin MICs elevated above wild-type values but still within internationally accepted breakpoints (BPs). A growing body of published studies now identify such strains as the norm and also that clinical response in serious infection is impaired. It has to be accepted, however, that this is a very controversial area. MIC testing systems are at their limit of sensitivity and there is little clinical evidence that increasing vancomycin dose to improve PK/PD target attainment has any beneficial effect. Vancomycin is however, perceived by many to be at the end of its useful life for treating serious infections. Its therapeutic ratio is now just too narrow. Recent IDSA guidelines fail to acknowledge this situation, however.

New drugs such as linezolid and daptomycin are making significant inroads into clinical use but both are troubled by early reports of resistance, some of it plasmid mediated. Old drugs too are also being used increasingly, but resistance is an emerging issue here too.

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Resistance to agents for MRSA decolonization and its clinical implications

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In most parts of the world, methicillin-resistant *Staphylococcus aureus* (MRSA) infection have continued to increase despite intensive infection-control efforts. Some groups have advocated "search and destroy" policies that recommend routine screening for MRSA to identify, isolate, and treat carriers, with the ultimate goal of eradicating the pathogen from health care facilities. All MRSA carriers are not the same; carriage may be transient, intermittent, or persistent for months to years. Persistent carriers are more heavily colonized (frequently at multiple sites), are more likely to transmit to others, and are more likely to become infected than transient carriers. Methods to eradicate MRSA have included the use of oral antibiotics plus rifampin. The use of rifampin ensures excellent penetration into secretions and tissues. The use of combination therapy has been effective in treating MRSA in the nares and at other sites. However, the wide-scale use of systemic antibiotics has been associated with the development of drug resistance and the loss of valuable therapeutic agents for subsequent treatment of infection. As a result of this drug-resistance issue, topical antibacterial agents and germicides have been the preferred intervention for MRSA eradication programs. Therefore, chlorhexidine and/or mupirocin to decolonize patients. Increased mupirocin use has been associated with increased drug resistance and failure to clear the organism. The gene for high-level mupirocin resistance, *mupA*, suggesting that the future usefulness of this drug might limited. Increased resistance of MRSA to systemic antibiotics following decolonization regimens has also been an issue in this study and others. Resistance to other germicides in MRSA has been reported following wide-scale use; whether resistance to chlorhexidine and its clinical implications will become an issue is not yet known. In this presentation, I will discuss decolonization strategy, resistant to agents for MRSA decolonization and its clinical implications.

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PK/PD considerations when treating MRSA

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Treatment of MRSA infections may often represent a life-threatening challenge and clinicians should be confident and apply the most advanced pharmacokinetic/pharmacodynamic (PK/PD) knowledge. There are in fact extensive data showing that the administration of antimicrobials according to PK/PD parameters improves the possibility of a positive clinical outcome, particularly in severely ill patients.

The three main PK/PD parameters able to predict antimicrobial efficacy are the maximum concentration (Cmax)/minimum inhibitory concentration (MIC) ratio, the area under the concentration-time curve (AUC/MIC) ratio and the time during which the drug concentration exceeds the MIC (T>MIC). The relative importance of the three PK/PD parameters varies according to different antimicrobial classes, and sometimes overlaps.

Moreover, critically ill patients require great attention in terms of dosages, posology and administration route of antimicrobials due to the many pathophysiological changes occurring during a severe acute illness or sepsis (i.e. increased capillary permeability, third spacing, increase of volume of distribution, variation of renal or liver function). All these factors may affect a drug's pharmacokinetics, especially the hydrophilic, renally excreted antibacterials (e.g. b-lactams, aminoglycosides and glycopeptides). Therefore, the serum and tissue concentrations achieved when these drugs are administered at dosages suggested for healthy volunteers are often suboptimal. The pharmacological strategies to be used in these patients are, for example, to increase doses and/or time of infusion